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PATENT

### Docket No.: 19603/2595 (CRF D-2400)

			)
Applicants	:	Hempstead et al.	) Examiner: ) Gary B. Nickol
Serial No.	:	09/830,520	
Cnfrm. No.	:	9715	) Art Unit: ) 1642
Filed	:	October 28, 1999	) )
For	:	METHODS FOR REGULATING ANGIOGENESIS AND VASCULAR INTEGRITY USING TRK RECEPTOR LIGANDS	) ) ) )

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#### DECLARATION OF JOSEPH A. MADRI UNDER 37 C.F.R. § 1.132

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

#### Dear Sir:

- I, Joseph A. Madri, pursuant to 37 C.F.R. § 1.132, declare:
- 1. I hold a B.S. degree and an M.S. degree from St. John's University, Jamaica, New York in Biology as well as a Ph.D. in Chemistry and an M.D. from Indiana University, Bloomington, Indiana
- 2. I am a Professor in the Department of Pathology at Yale University School of Medicine, New Haven, Connecticut.
- 3. As demonstrated in my Curriculum Vitae (attached hereto at Exhibit 1), I have extensive expertise in the area of angiogenesis. In particular, my areas of research have included angiogenesis, angiogenic growth factor biology, connective tissue biophysics, biochemistry and cell biology, vascular biology, vascular development, neurovascular development, cardiovascular development, and immunology.
- 4. I have reviewed the above patent application and U.S. Patent No. 5,733,871 to Alps et. al., ("Alps") and am providing this declaration to explain the why Alps' method of treating neuronal damage would not have suggested to scientists in the field that

the trk receptor ligands, brain derived neurotrophic factor ("BDNF"), NT-3, or NT-4, would be useful in inducing angiogenesis, as described in the present application.

- 5. Alps relates to the treatment of neuronal damage in the central nervous system of individuals in need of such treatment. In particular, Alps relates to intravenous administration of pharmaceutically acceptable compositions of neurotrophic factors, such as bFGF, aFGF, NGF, CNTF, BDNF, NT3, NT4, IGF-I, and IGF-II, for treating or preventing neuronal damage as a consequence of ischemia, hypoxia, or neurodegeneration. Thus, Alps relates to administration of neurotrophic factors which target neurons to improve survival and limit damage.
- 6. Nowhere does Alps disclose inducing angiogenesis in a patient that has cardiac ischemia or a vascular disorder by administering BDNF, NT-3, or NT-4. In its examples, Alps uses focal or global ischemia models to induce neuronal damage. However, such models are used to create the symptom that Alps is interested in treating—i.e. neuronal damage. There is no indication in Alps that the underlying condition causing neuronal damage in Alps is being treated or is capable of being treated in accordance with the present application. There is also no indication that Alps is inducing angiogenesis with BDNF, NT-3, or NT-4 as in the invention of the present application. All Alps is doing with these neurotrophic factors is what was well known in the art to use them for—treating neuronal conditions.
- 7. The invention of the present application goes beyond the known use of such factors and involves the discovery that BDNF, NT-3, and NT-4 can be used for the very different purpose of inducing angiogenesis.
- 8. The factors that Alps identifies as neurotrophic factors are wide ranging and, while they include BDNF, NT-3, and NT-4, they go well beyond them. Indeed, the bulk of the experimental work set forth in Alps is with bFGF which, unlike BDNF, NT-3, and NT-4, is not a trk receptor ligand. In the sentence bridging columns 4 and 5 of Alps, it is stated that "[s]ome neurotrophic factors are also capable of promoting neurite outgrowth and glial cell and blood vessel restoration or inducing cells to secrete other neurotrophic factors (emphasis added)." However, in column 9, lines 39-49 of Alps, it is made clear that, with regard to promoting blood vessel formation, Alps is only talking about bFGF. Alps's acknowledgement that bFGF achieves angiogenesis is no surprise, because the ability of bFGF to do so was well known in 1999.
- 9. What was not known even when the present application was filed in 1999 was that BDNF, NT-3, or NT-4 have the ability to promote blood vessel formation.

P.04

- 3 -

These molecules, at that time, were regarded as neurotrophic factors having no relevance to inducing angiogenesis. Thus, the indication in Alps (column 9, lines 42-45) that the non-trk receptor ligand, bFGF, is a potent "'gliotrophic' factor that promotes the proliferation of brain glial cells (including astroglia and oligodendroglia), as well as an 'angiogenic' factor that promotes the proliferation of brain capillary endothelial cells and blood vessels" was limited to bFGF. This statement would not have suggested to those in the field that BDNF, NT-3, or NT-4 are useful in promoting angiogenesis.

- For all of these reasons, I, like others skilled in the area of 10. angiogenesis, reading Alps would not have not have regarded it as teaching that BDNF, NT-3, or NT-4 would be useful in inducing angiogenesis.
- I hereby declare that all statements made herein of my own knowledge are 11. true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 7/20/04

Joseph A. Madri, M.D., Ph.D.

7/7/04

#### **CURRICULUM VITAE**

Name:

Joseph A. Madri

Date and Place of Birth:

May 16, 1946; New York, New York

Married, Two children

Education: 1959-1963 1963-1967 1967-1969 1969-1973 1973-1975 1975-1977	Archbishop Molloy High School, Jamaica, New York St. John's University, Jamaica, New York, B.S. in Biology St. John's University, Jamaica, New York, M.S. in Biology Indiana University, Bloomington, Indiana, Ph.D. in Chemistry Indiana University, Indianapolis, Indiana, M.D. Resident in Anatomical Pathology, Yale-New Haven Hospital, New Haven, CT Fellow in Pathology, Yale University School of Medicine, New Haven, CT		
Career:			
1967-1969	NSF Traineeship, St. John's University		
1969-1970	Associate Instructor, Indiana University		
1970-1971	Research Associate, Indiana University		
1971-1972	Research Assistant, Indiana University		
1972-1973	NIH Traineeship, Indiana University American Lung Association Student Fellowship, Indiana University		
1975	Resident, Department of Pathology, Yale University Medicine		
1975-1977	USPHS Individual Research Fellowship Award, Yale University		
1977-1980	Assistant Professor Department of Pathology, Yale University School of Medicine		
1980-1985	Co-director, Immunohistochemistry Laboratory, Department of Pathology, Yale		
1980-1984	Linite consists Cohool of Medicine		
1985-1991	Associate Professor, Department of Pathology, Yale University School of Medicine		
1000	Tonuro		
1001_present	Professor, Department of Pathology, Yale University School of Medicine and The		
1991-present	Graduate School of Arts & Sciences		
	Co-director of the Reed Foundation Fellowship in Vascular Biology		
1992-present	Discrete of Madical Studios, Pathology		
1992-present	Founding Scientist & Member, Board of Directors, Alexion Pharmaceuticals, Inc., New		
1002 process	Haven CT.		
1992-2000	Chairman, External Scientific Advisory Board, Alexion Pharmaceuticals, Inc., New		
,,,,,,	Haven CT		
1992-1998	A Annahar Chrimnoro Hospitals Research Advisory Board		
1994-1999	Member, Scientific Board of Directors, Genzyme Tissue Repair, Inc. Framingham,		
	MA.		

#### **Medical Licenses:**

Indiana #01026304 08/06/75 to 06/30/82 Connecticut #022381 1979 to present

#### **Societies and Honors:**

Sigma Xi
Phi Lambda Upsilon
American Chemical Society
American Association of Pathologists
International Academy of Pathology
American Society for Cell Biology
New York Academy of Science
Diplomate - American Board of Pathology 1979
Member, Editorial Board of "Arteriosclerosis" 1983 to 1999

Member, Editorial Board of "American Journal of Pathology" 1984 to 1992 Associate Editor, "American Journal of Pathology" Jan. 1992 to May 1996 Member, Editorial Board of "Laboratory Investigation" July, 1991 to 1995 Executive Editor, "Laboratory Investigation" July, 1995 to Sept., 2003

Member, Editorial Board of "Angiogenesis" 1997 to Present Member, Editorial Board of "Endothelium" 1999 to Present

Associate Editor, "FASEB J." 2002 - present

Reviewer for the Pathology A and Pathobiological Chemistry Study Sections, The Dental Institute, The Cancer Institute, The Atherosclerosis SCOR, Senior Fellowships Special Study Section and Developmental Cardiobiology Program Projects Study Section of The National Institutes of Health at various times from 1983 to Present

Black Belt-First Dan, TaeKwon-Do 1991

Member, American Heart Association, Study Section on Vascular Wall Biology 1991-1994

Member, Research Advisory Board of the Shriners Children's Hospitals, 1992-1998 Councilor, American Society of Investigative Pathology, July, 1993 to July, 1996

Black Belt-Second Dan, TaeKwon-Do 1997

MERIT Award from NHLBI-NIH 2/99

Black Belt-Third Dan, TaeKwon-Do 2000 Chugai Award for Meritorious Mentorship & Scholarship from the Amer. Soc. Invest. Pathol., 4/2001

Black Belt-Fourth Dan, TaeKwon-Do 2003

#### Areas of Interest/Expertise:

Vasculogenesis & Angiogenesis

**Biology and Biochemistry of Connective Tissues** 

Cell Biology of Endothelial and Vascular Smooth Muscle Cells

**Cell-Matrix Interactions Immunopathology** 

Light and Electron Microscopy and Immunoelectron Microscopy

**Trainees To Date:** 

PostDoctoral:

37 Ph.D. Thesis: 11

M.D. Thesis:

9

Undergraduate: 20

#### **Current Support:**

R37-HL28373-22

The Pathology of Endothelial Neovascularization

Current

Annual Direct Costs: \$297,530.00

MERIT Award

Duration: 3/99 to 2/09

Principal Investigator: J.A. Madri

Effort: 25%

RO1-HL51018-08

Proteinase modulation during T cell-endothelial adhesion

Current

Annual Direct Costs: \$225,000.00

Duration: 4/01 to 3/05

Principal Investigator: J.A. Madri

Effort: 20%

PO1-DK38979-10

Cell and Molecular Pathobiology of Renal Disease

Current

Project 1: Renal microvascular endothelial cell differentiation

Annual Direct Costs: \$139,944.00

Duration: 7/93 to 11/04

Principal Investigator: J.A. Madri

Effort: 20%

PO1-NS35476-07

Adaptive Mechanisms of Developing Brain

Current

Project 1: Cellular and Molecular Basis of Angiogenesis in the

**Developing Brain** 

Annual Direct Costs: \$165,850.00

Duration: 2/03 to 6/08

Project 1 Principal Investigator: J. A. Madri

Effort: 20%

T32 DK07556-17

**Experimental Pathobiology Training Grant** 

Current

Annual Direct Costs: \$116,232.00 Duration: 7/77 to 6/07

Principal Investigator: J. S. Morrow

Effort: 5%

Reed Foundation

Postdoctoral Fellowship in Vascular Biology

Current

Annual Direct Costs: \$30,000.00 Duration: 1/92 to 06/2004

Co-Director (with Dr. L. Bell): J.A. Madri

RO1-HL51018-08 Pending

Proteinase modulation during T cell-endothelial adhesion

Annual Direct Costs: \$250,000.00

Duration: 4/05 to 3/09

Principal Investigator: J.A. Madri

Effort: 20%

1) Genetically engineered endothelial cells exhibit enhanced migration and plasminogen activator Aug. 9, 1994 USA # 5,336,615

activity 2) Universal Donor Cells

USA # 5,705,732

Jan. 6, 1998

3) Universal Donor Cells

Europe #00114262.9-2105

Aug. 29, 2000

Publications (203)

- 1. Madri, J.A. Carboxypeptidase A: Solvent and ion effects. Ph. D. Thesis, Indiana University, 1973.
- 2. Madri, J.A., Fromowitz, F.B. Amyloid deposition in immunoblastic lymphadenopathy. Human Pathol., 9: 157-162, 1978.
- 3. Marier, R., Valenti, A.J., Madri, J.A. Gram-negative endocarditis following cystoscopy. <u>J. Urol.</u>, 119: 134-140, 1978.
- 4. Stenn, K.S., Madri, J.A., Roll, F.J. Migrating epidermis produces AB<sub>2</sub> collagen and requires continual collagen synthesis for movement. Nature, 277: 229-232, 1979.
- 5. Madri, J.A., Furthmayr, H. Isolation and tissue localization of type AB<sub>2</sub> collagen from normal lung parenchyma. Am. J. Pathol., 94: 323-331, 1979.
- 6. Roll, F.J., Madri, J.A., Furthmayr, H. A new method of iodinating collagens for use in radioimmunoassay. Anal. Biochem., 96: 489-499, 1979.
- 7. Madri, J.A., Furthmayr, H. Collagen polymorphism in the lung: An immunochemical study of pulmonary fibrosis. Human Pathol., 11: 353-366, 1980.

- 8. Roll, F.J., Madri, J.A., Albert, J., Furthmayr, H. Codistribution of collagen types IV and AB<sub>2</sub> in basement membranes and mesangium of the kidney: An immunoferritin study of ultrathin frozen sections. J. Cell Biol., 85: 597-616, 1980.
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- 14. Engel, J., Ordermatt, E., Engel, A., Madri, J.A., Furthmayr, H., Rohde, H. and Timpl, R. Shapes, domain organizations and flexibility of laminin and fibronectin, two multi-functional proteins of the extracellular matrix. <u>J. Mol. Biol.</u>, 150:97-120, 1981.
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- 18. Madri, J.A. The Preparation of Type V Collagen, in <u>The Immunochemistry of the Extracellular Matrix</u>, Vol. I, edited by H. Furthmayr, CRC Press, Boca Raton, Florida, p. 75-90, 1982.
- 19. Roll, F.J., Madri, J.A. Immunocytochemical Techniques in Connective Tissue Research in <a href="https://doi.org/10.10/10/10.15">The Immunochemistry of the Extracellular Matrix</a>, Vol. II, edited by H. Furthmayr, CRC Press, Boca Raton, Florida, p. 49-88, 1982.
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- 22. Madri, J.A., Stenn, K.S. Aortic Endothelial Cell Migration: I. Matrix requirements and composition. Am. J. Pathol., 106: 180-186, 1982.
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- 47. Ingber, D.E., Madri, J.A., Jamieson, J.D. Basement membrane as a spatial organizer of polarized epithelia: Exogenous basement membrane reorients pancreatic epithelial tumor cells in vitro. <a href="https://example.com/membrane/47.122:129-139">Amer. J. Pathol., 122:129-139</a>, 1986.
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- 203. Biswas, P., Zhang, J., Schoenfeld, J., Schoenfeld, D., Gratzinger, D., Canosa, S., Madri, J.A., Interactions and identification of the regions of PECAM-1 involved in β- and γ-catenin associations and their biological significance, Submitted, 2004.
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#### **Committee Work**

Member - Department Safety Committee, 1980-1983

Member - Housestaff Selection Committee, 1980-1987 & 1989-1993

Member - Medical Student Pathology Course Committee, 1980-Present

Member - Graduate Student Program Committee, 1983-Present

Member - MD/PhD Student Advisory and Admissions Committee, 1986-Present

Member - Miles Seminar Series Program Committee, 1984-1986

Chairman - Pathology Department Research Seminar Series Committee, 1981-1987

Chairman - Departmental Medical School Thesis Committee, 1982-1985

Chairman - Departmental Photographic Services Committee, 1985-1987

Director of Graduate Studies, Experimental Pathology, 1986-1987

Member - American Cancer Society Institutional Research Grant Review Committee, 1988-1990

Member - FASEB-AAP Program committee, 1988-1990

Chairman - Pathology Search Committee - in Pediatric & Neonatal Pathology, 1989-1990

Co-Chairman - Yale University Center of Molecular Medicine Cardiobiology Advisory Group, 1989-1991

Member - Yale University Planning & Priorities Committee, 1990 - 1993

Director of Medical Studies: Pathology - 1992- Present

Member - Yale University Basic Sciences Curriculum Subcommittee - 1992 - Present

Member - Yale University Education Policy & Curriculum Committee - 1996 - 1998

Councilor - American Society of Investigative Pathology, 7/1/93 to 6/30/96

Member - ASIP Committee on Career Development, Women & Minorities, 7/1/93 to 6/30/96

Member - Pathology Department Executive Committee, 2/99 to present

Member - Yale University Senior Appointments and Promotions Committee, 1999 - 2002

Chair - Anna Fuller Foundation Fellowship Selection Committee at Yale, 2000 - Present

Member - ASIP Meritorious Awards selection committee, 2002 to present

#### Presentations at National and International Meetings:

Gordon Conference - Structural Macromolecules. Collagen. Speaker, "Endothelial Cell Collagen Biosynthesis: Structure/Function Relationships." Santa Barbara, CA, 2/80.

Gordon Conference - Structural Macromolecules. Collagen. Speaker, "Monoclonal Antibodies to Type IV Collagen: Molecular Probes." Plymouth, NH, 7/81.

FASEB Symposium Chairman & Speaker. "Immunochemistry of the Extracellular Matrix." New Orleans, LA, 4/82.

Symposium, The Extracellular Matrix: Chemistry, Biology, Pathology. Speaker, "Collagen Immunology and Immunochemistry." Washington University, St. Louis, 6/82.

Conference on: The biology of Inflammation, Cell-Cell Interactions and Connective Tissue: Potential New Approaches to Atherosclerosis Research. Speaker, "Endothelial Cell-Matrix Interactions in Hemostasis and Angiogenesis." NIH, Washington, DC, 9/82.

Gordon Conference - Atherosclerosis. Speaker, "Endothelial Cell-Matrix Interactions: The Role of Matrix in Angiogenesis." Meriden, NH, 6/83.

Gordon Conference - Structural Macromolecules - Collagen. Speaker, "Capillary Endothelial Cell Cultures: Phenotypic Modulation by Extracellular Matrix." Plymouth, NH, 7/83.

CIBA Foundation Symposium. Basement Membranes and Cell Movement. Speaker, "The Structure and Organization of Basement Membranes." London, U.K., 1/84.

FASEB Symposium - Matrix Aspects of Wound Healing. Speaker, "The Role of Matrix in Modulating the Angiogenic Response." St. Louis, MO, 4/84.

Biology of the Vascular Endothelial Cell: Third International Symposium. Speaker, "Endothelial Cell: Cytoskeletal-Matrix Interactions." Boston, MA, 6/84.

Cellular and Molecular Organization of Epithelia, British Society of Cell Biology. Speaker, "Endothelial cell-Matrix Interactions in Large Vessel and Microvascular Endothelium." Kent, England, 9/84.

Biology, Chemistry and Pathology of Collagen, N.Y. Academy of Sciences Symposium. "Endothelial Cell-Extracellular Matrix Interactions." New York, NY, 10/84.

FASEB Symposium Co-Chairman & Speaker. "Plasma Membrane Interactions with the Cytoskeleton and Exoskeleton." Anaheim, CA, 4/85.

Histochemical Society Annual Meeting, Invited Lecture: "Endothelial Cell-Matrix Interactions: In Vitro Models of Angiogenesis." Washington, DC, 5/85.

Gordon Conference - Atherosclerosis. Speaker, "Endothelial Cell Proteoheparin Sulfate Metabolism: Modulation by Matrix." Meriden, NH, 6/85.

Gordon Conference - Structural Macromolecules. Collagen. Chairman & Speaker - Session on The Pathology of Connective Tissues. Plymouth, NH, 7/85.

NIH Symposium on: Perspectives in Endothelial Cell Biology. Speaker, "Cytoskeletal-Matrix Interactions of the Endothelium." Washington, DC, 12/85.

FASEB Symposium Chairman & Speaker. "Extracellular Matrix-Cytoskeleton-Membranes." St. Louis, MO, 4/86.

George Washington University Sixth Annual International Spring Symposium: Cardiovascular Disease '86: Molecular and Cellular Mechanisms, Prevention, Treatment. Speaker, "The Extracellular Matrix as a Modulator of Neovascularization." Washington, DC, 5/86.

University of Iowa, Pulmonary Disease Division, Boehringer-Ingelheim Lecturer, Iowa City, Iowa, 11/6-7/86.

Gordon Conference - Cell Contact and Adhesion Speaker, "Endothelial Cell-Matrix Interactions: Microvascular Endothelial Cells." Tilton, H.H., 6/87.

Distinguished Lecture Series, The Cellular and Molecular Biology Component of ASEND, University of North Dakota, Lecturer, "Microvascular Endothelial Cells: Modulation by Extracellular Matrix." Grand Forks, N.D., 9/27-29/87

Tissue Culture Association Annual Meeting, Invited Lecture: "Interactions of Soluble (TGF-β) and Solid Phase (Matrix) Factors in Angiogenesis." Las Vegas, NV, 6/12-15/88.

Gordon Research Conference on Vascular Cell Biology, Speaker, "Endothelial Cell Modulation by Solid Phase (Matrix) and Soluble Factors (TGF-β)." Meridian, N.H., 7/31/88 - 8/5/88.

Vth Workshop of The Swiss Association Against High Blood Pressure, "The Vascular Smooth Muscle Cell". Lecture Title: "Interactions of Soluble and Solid Phase Factors in Arterial and Capillary Endothelial Cells". Montreux, Switzerland, 10/2/88 - 10/4/88.

FASEB Symposium Chairman & Speaker. "Adhesive Proteins and Matrix Interactions in Vascular Cells" New Orleans, LA, 3/89.

AASLD Asilomar Conference on Connective Tissue Biology of the Liver. Speaker, "Endothelial cell responses to injury: Modulation by matrix and soluble factors" Asilomar, CA, 4/16 to 4/19/89.

Biology and Chemistry of Transforming Growth Factor Beta, N.Y. Academy of Sciences Symposium. Speaker, "The Effects of TGF- $\beta$ 1 and  $\beta$ 2 on Vascular Cells" Bethesda, MD, 5/18 to 5/20/89.

Workshop on the Biology of the Renal Microvasculature, Speaker, "Cell-Basement Membrane Interactions in Control of Growth and Differentiation" National Institutes of Health, Bethesda, MD, 10/23/89 to 10/24/89.

Endothelial Cells in Development and Disease, Speaker, "Regulation of Endothelial Cell Function by Extracellular Matrix", National Institutes of Health, Crystal City, VA, 11/19/89 to 11/21/89.

The Biology of Sarcomas, UCLA symposium, Co-organizer, Session Chairman and speaker "Interactions of tumor cells, host stromal cells and the extracellular matrix", Lake Tahoe, CA, 3/11/90 to 3/16/90.

The Endothelial Cell/Tissue Engineering, Joint UCLA symposia, Joint meeting, Session Chairman and speaker "Endothelial cell phenotypes" Keystone, CO, 4/6/90 to4/12/90.

First Altschul Symposium, Atherosclerosis: Cellular and molecular interactions in the artery wall, Organizing committee member and Speaker, "Soluble factor and matrix modulation of vascular cell phenotype", Saskatoon, Saskatchewan, Canada, 4/29/90 to5/2/90.

American Lung Assoc., American Thoracic Society World Conf. on Lung Health, Invited speaker in Cellular and extracellular regulation of pulmonary vascular growth and development, "Extracellular matrix composition and organization as a modulator of microvascular endothelial cell phenotype, Boston, MA, 5/20/90 - 5/24/90.

Second Gordon Research Conference on Vascular Cell Biology, Session chairman and Speaker on vascular cells and extracellular matrix, "Vascular Cell Phenotypic Modulation by Solid Phase (Matrix) and Soluble Factors." Meridian, N.H., 7/29/90 - 8/3/90.

Workshop on "Development of Cell Lines for Hypertension Research" Invited Speaker, "The role of the extracellular matrix and soluble factors in modulating vascular cell behavior", National Institutes of Health, Bethesda, MD, Feb. 19 & 20, 1991

FASEB Symposium Co-Chairman & Speaker. "Cell-Cell Interactions in Vascular Cells" Atlanta, GA, April, 1991.

24<sup>th</sup> Annual Lofland Conference, Speaker: Speaker, "Positive and Negative Modulators of Endothelial Cell Migration", Seattle, WA, May 22 to 26, 1991.

International Society of Nephrology Sponsored Symposium "Forefronts in Nephrology - Biology of the Glomerular Mesangium", Co-Organizer and Speaker, "Matrix-Driven Growth Factor Receptor Modulation of Vascular Cells", Kloster Banz, F. R. Germany, June 9 to 12, 1991.

MCDB/ISU Symposium on Transforming Growth Factor- $\beta$  and Related Proteins in Development, Speaker: "Modulation of Vascular Cell Behavior by Transforming Growth Factors- $\beta$ ", Ames, Iowa, September 20 to 23, 1991.

The Molecular Biology of the Endothelial Cell, UCLA symposia, Joint meeting, Session Chairman and Speaker "Endothelial cell phenotypes" Keystone, CO, 1/13/92 to1/17/92.

American Heart Association Meeting on Vascular Cell Biology, Speaker, "Fibronectin alternate splicing in vascular cells: Functional Significance", SnowBird, Utah, 1/29/92 to 2/1/92.

FASEB-APS Society Symposium Speaker. Cellular and Molecular Biology of the Endothelial Cell, "The inter-relationships between growth factors and extracellular matrix components in angiogenesis and neovascularization", Anaheim, CA, April 5 to 10, 1992.

Third Gordon Research Conference on Vascular Cellular and Molecular Biology, Meeting Co-Chairman and Speaker, The role of PECAM-1 (CD31) in modulating endothelial cell migration", Meridian, N.H., 6/29/92 to 7/3/92.

Upjohn Brook Lodge Workshop Speaker, "A new understanding of the role of matrix metalloproteinases in tumor biology", Invited Participant, Augusta MI, 9/27/92 to 9/29/92.

Biology of the Vascular Endothelial Cell: VII International Symposium on the Biology of Vascular Cells. Speaker, "Endothelial Cell-Matrix Interactions." San Diego, CA, 11/10/92 to 11/14/92.

American Heart Association, 10<sup>th</sup> National Conference on Thrombosis and Hemostasis, Speaker, "Factors that enhance and inhibit endothelial cell migration", New Orleans, LA, 11/18/92.

Cell Adhesion Mechanisms in Leukocyte Traffic, UCLA symposia, Joint meeting, Session Chairman and Speaker "Microvascular Endothelial cell Differentiation" Keystone, CO, 1/24/93 to1/31/93.

Tissue Regeneration Workshop, Invited Speaker, "Extracellular Matrix Modulation of Endothelial Cell Phenotype During Angiogenesis", Princeton, NJ, Johnson & Johnson, 3/9 & 10/93.

Endothelial Changes in Age-Related Vascular Disease Workshop, National Institute on Aging, Invited Speaker, "Matrix Organization and Endothelial Differentiation", Bethesda, MD, 4/26 & 27/93.

American Heart Association, Conference on Molecular and Cellular Biology of Vascular Cells, Speaker, "The Role of T cell Proteinases in Transmigration", Boston, MA, 10/15/93 to 10/17/93.

Molecular Biology of the Endothelial Cell, UCLA symposia Speaker, "Microvascular Endothelial cell Differentiation" Keystone, CO, 1/16/94 to 1/23/94.

FASEB-ASIP Society Symposium Speaker. Tissue Repair and Regeneration, "The role of c-src in endothelial cell signal transduction during migration and angiogenesis", Anaheim, CA, April 24 to 29, 1994

FASEB-ASIP Society Symposium Co-Chairman & Speaker (with Dr. Marlene Rabinovitch). Extracellular Matrix in the Vessel Wall, "Extracellular Matrix Mediated Signalling in Vascular Cells Following Injury", Anaheim, CA, April 24 to 29, 1994.

Fogarty International Center Conference on TGF-βs: Biological Mechanisms and Clinical Applications, Speaker, "The Modulation of Vascular Cells by TGF-βs", Nat'l. Institutes of Health, Bethesda, MD., May 4-6, 1994.

 $4^{th}$  Gordon Research Conference on Vascular Cellular and Molecular Biology, Speaker, "Engagement of  $\alpha 4\beta 1/VCAM-1$  Elicits T cell Proteinase Induction during Transmigration", Meridian, N.H., 6/13/94 to 6/19/94.

2nd Franz Volhard Symposium on "Mechanisms of Angiogenesis", Speaker, "Cell-Matrix Interaction in Angiogenesis" Max-Delbruck Center, Berlin, Germany, 5/25/95 to 5/28/95.

Gordon Research Conference on Cell Adhesion, Speaker, "Specific integrin mediated signalling", Andover, N.H., 6/11/95 to 6/15/95.

Gordon Research Conference on Matrix Metalloproteinases, Speaker, "Engagement of  $\alpha 4\beta 1/VCAM-1$  Elicits T cell Proteinase Induction during Transmigration", Andover, N.H., 7/16/95 to 7/21/95.

International Symposium: New Frontiers in Infection, Inflammation and Autoimmunity, Speaker, "Integrin-Mediated Proteinase Induction: Its role in T cell Transendothelial Migration", Atezelsberg Castle, Erlangen, Germany, 11/30/95 to 12/3/95.

Wound Healing in Context/Tissue Engineering, UCLA symposia, Joint meeting, Session Chairman and Speaker "Extracellular matrix modulation of Microvascular Endothelial cell TGFβ receptor expression" Taos, NM, 1/23/96 to1/28/96.

American Association for Cancer Research Special Conference: Proteases and Protease Inhibitors, Speaker "The roles of adhesion molecules and proteinases in lymphocyte transendothelial migration", Panama City, FL, 3/2/96 to 3/5/96.

FASEB-NAVBO/ASIP Society Symposium Co-Chairman & Speaker (with Dr. Tim Hla). Vascular Cell and Molecular Biology, "Extracellular Martix Mediated Signalling in Vascular Cells", New Orleans, LA, 5/31/96 to 6/4/96.

Sixth World Congress for Microcirculation, Session Co-chairman and Speaker: The Extracellular Matrix as a Modulator of Vascular Growth - "Modulation of Endothelial Cell Phenotype by Matrix", Munich, Germany, 8/25/96 to 8/29/96.

Twelfth International Symposium on Cellular Endocrinology "The Extracellular Matrix: Its Synthesis, Function and Degradation", Speaker: "Adhesion molecules and proteinases in T cell transendothelial migration", Lake Placid, New York, 9/12/96 to 9/15/96.

Second International Symposium on the Etiology and Pathobiology of Transplant Vascular Sclerosis, Chair & Speaker, Plenary Session IV: Cell-Matrix Interactions, "Extracellular Matrix Modulation of Vascular Cell Behavior", Bermuda Southampton Princess Resort, Bermuda, 3/5-3/9/97.

Gordon Research Conference on Angiogenesis and Microcirculation, Speaker, "Matrix-driven integrin-mediated PECAM-1 tyrosine dephosphorylation during vasculogenesis and endothelial cell migration" Salve Regina College, Newport, RI, 08/17/97 to 08/22/97.

Thirteenth International Symposium on Cellular Endocrinology "The Development of the Vascular System", Speaker: "PECAM-1 (CD31) tyrosine phosphorylation and signaling in vasculogenesis and angiogenesis" Lake Placid, New York, 9/11/97 to 9/14/97.

Cardiovascular Function Symposium, American Heart Association, Speaker: "The role of PECAM-1 in vasculogenesis and angiogenesis" Lake Tahoe, CA, 2/22/98 to 2/25/98.

Endothelium/Molecular Mechanisms of Leukocyte Trafficking, Joint UCLA symposium, Speaker "Vascular differentiation during post-natal neural development", Lake Tahoe, CA, 3/21/98 to 3/28/98.

NHLBI/ATS Workshop on the Molecular and Genomic Effects of Tissue Oxygen Deprivation in Sleep Apnea. Speaker: "Hypoxia-Induced Brain Angiogenesis", Bethesda, MD, 9/24/98 to 9/25/98.

University of Toronto, Faculty of Medicine, Department of Laboratory Medicine and Pathobiology, Keynote Speaker, Research Day, Toronto, Canada, 2/1/99.

International Society for Heart Research Symposium, Speaker: "PECAM-1 and Angiogenesis", San Diego, CA, 6/9/99 to 6/12/99.

Gordon Research Conference on Angiogenesis and Microcirculation, Poster Presenter, "PECAM-1 is a reservoir for and a modulator of  $\beta$ -catenin" Salve Regina College, Newport, RI, 08/15/99 to 08/20/99.

New York Academy of Medicine conference: Angiogenesis-Research Frontiers, Invited Speaker: "Differential tyrosine and serine phosphorylation of endothelial PECAM-1 modulates association with  $\beta$ – and  $\gamma$ -catenins and SHP-2: Implications for angiogenesis", New York City, NY, 1/10/00.

FASEB-ASIP Society Symposium Speaker. Symposium: Regulation of Vascular Cell Growth by Extracellular Matrix, Lecture Title: "PECAM-1: A modulator of junctional, adhesive, migratory and proliferative activities", San Diego, CA, 4/14/00 to 4/19/00.

FASEB-ASIP Society Chugai Award Recipient and Invited Chair & Speaker. Chugai Symposium: Lecture Title: "PECAM-1: A multidomain/multifunctional protein with diverse signaling and scaffolding properties - Implications for angiogenesis and inflammation", Orlando, FL, 3/31/01 to 4/4/01.

University of Illinois, Chicago, Medical School, DeTrana Lecture in Pathology, "PECAM-1: A multidomain/multifunctional protein with diverse signaling and scaffolding properties - Implications for angiogenesis and inflammation" April 23, 2001.

Gordon Research Conference on Matrix Metalloproteinases Speaker: "Matrix Metalloproteinases and vascular control: new paradigms", Il Chocco, Tuscany, Italy, 5/13/01 to 5/18/01.

National Multiple Sclerosis Society Round Table Discussion - Invited Panelist "Strides and Stumbles in MS", Hartford, CT, 6/26/01.

FASEB-ASIP Society Symposium Co-Chair & Speaker. Proteases, Matrix and Proteoglycans: Lecture Title: "Coordinate Control of MT1-MMP and MMP-2 Expression During Angiogenesis: The roles of Egr-1, Sp1 and AP1", New Orleans, LA, 4/21/02 to 4/24/02.

Third Ringberg Conference on Molecular Mechanisms of Leukocyte Traffic, Invited Speaker, "CD31: A modulator of vascular and leukocyte function" Ringberg, Germany, 9/22/02 to 9/25/02, 2002.

American Society For Cell Biology 42<sup>nd</sup> Annual Meeting, Co-Chair and Speaker, Minisymposium: "Cell Biology of Angiogenesis", San Francisco, CA, 12/14/02 to 12/18/02.

New Therapeutic Targets in Vascular Biology, Invited speaker: "The inter-related roles of VEGF, PECAM-1 and MMP-2 in cardiac cushion development", Geneva, Switzerland, 2/6/03 to 2/9/03.

Novo Nordisk Foundation Consortium 5<sup>th</sup> Annual Conference on "Vascular Biology in Complications of Diabetes" Invited speaker; "Maternal Diabetes: Effects of on embryonic vascular development – a VEGF-A mediated process". Tammsvik Conf. Ctr., Bro, Sweden, 5/16/03 to 5/18/03.

International Society on Thrombosis and Haemostasis – XIX Congress, Invited speaker: "Cell adhesion and Angiogenesis", Birmingham, UK, 7/12/03 to 7/18/03.

FASEB-ASIP Society Symposium Co-Chair & Speaker. Molecular and cellular basis of disease: Structure and function of the extracellular matrix in disease: Novel roles and regulation of MMPs and TIMPs in disease. Lecture Title: "Evidence for a cellular protease thermostat in health and disease", Washington, DC, 4/17/04 to 4/22/04.

XIII<sup>th</sup> International Vascular Biology Meeting, Invited Speaker, "PECAM-1 A dynamic multifunctional regulator of junctional integrity", Toronto, Canada, 6/1/04 to 6/5/04.